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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/884,526 | 06/19/2001 | David Meeker | 07680.0019.00000 | 2532 |

22852 7590 01/31/2005

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| EXAMINER | |
|---|---|
| CHEN, SHIN LIN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 01/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/884,526 | MEEKER ET AL. | |
| | Examiner | Art Unit | |
| | Shin-Lin Chen | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4 and 6-19* is/are pending in the application.

4a) Of the above claim(s) *2,3 and 7-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6 and 13-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicants' amendment filed 11-23-04 has been entered. Claim 4 has been amended. Claims 1-4 and 6-19 are pending. Claims 1, 4, 6 and 13-19 are under consideration.

### *Claim Rejections - 35 USC § 103*

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 4, 6 and 13-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schiffmann et al., January 2000 (PNAS, Vol. 97, No. 1, p. 365-370) or Desnick et al., 1979 (PNAS, Vol. 76, No. 10, pp. 5326-5330) each in view of Ziegler et al., 1999 (Human Gene Therapy, Vol. 10, No. 10, p. 1667-1682) and Selden et al., 1998 (WO 98/11206).

Claims 1, 4, 6 and 13-19 are directed to a method of reducing the accumulation of globotriaosylceramide in a subject having Fabry disease by administering to the subject an

exogenously produced natural or recombinant alpha-galactosidase A and a viral or non-viral vector encoding a alpha-galactosidase A so as to reduce the accumulation of globotriaosylceramide. Claims 13-15 specify the vector encoding a alpha-galactosidase A is administered before or after or simultaneously with the administration of the alpha-galactosidase A protein, respectively. Claim 16 specifies the alpha-galactosidase A protein is administered alternatively with the vector encoding a alpha-galactosidase A. Claim 17 specifies the alpha-galactosidase A protein is administered intravenously. Claims 18 and 19 specify the viral or non-viral vector encoding a alpha-galactosidase A is administered ex vivo and in vivo, respectively.

Shiffmann teaches infusing alpha-galactosidase A intravenously into 10 patients with Fabry disease and shows that the alpha-galactosidase A is identified in several cell types in the liver tissue 2 days after the enzyme infusion, and 9 out of 10 patients had significantly reduced globotriaosylceramide levels both in the liver and shed renal tubular epithelial cells in the urine sediment (e.g. abstract).

Desnick teaches administering splenic or plasma alpha-galactosidase isozyme intravenously into recipient with Fabry disease and shows that after each dose of splenic isozyme the concentration of globotriaosylceramide decreased maximally (50% of initial values) in 15 minutes and injection of plasma isozyme decreases the concentration of globotriaosylceramide 50-70% by 2-6 hours (e.g. abstract).

Shiffmann or Desnick does not teach combination of natural or recombinant alpha-galactosidase A protein with a vector encoding a alpha-galactosidase A for reducing the accumulation of globotriaosylceramide in a subject with Fabry disease. Schiffmann or desnick

does not teach administering the alpha-galactosidase A protein before, after, simultaneously, or alternately with a vector encoding alpha-galactosidase A to the subject.

Ziegler teaches preparation of an adenoviral vector encoding human alpha-galactosidase A (Ad2/CEHalpha-Gal) and injecting said adenoviral vector intravenously into Fabry knockout mice. Ziegler shows that alpha-galactosidase A activity is elevated in all tissues of the injected Fabry mice and significant reduction in GL-3 (globotriaosylceramide) content in all tissues is concomitant with the increase in enzyme activity (e.g. abstract).

Selden teaches that a patient with Fabry disease can be treated with either genetically modified human cells overexpressing and secreting human alpha-gal A (gene therapy) or with purified human alpha-gal A recombinant protein (enzyme replacement therapy) (e.g. p. 2 lines16-32). Selden states some advantages of gene therapy over enzyme replacement therapy, however, Selden states "individuals with alpha-gal A deficiencies may also be treated with purified alpha-gal A (i.e. enzyme replacement therapy)" (e.g. pages 4-5).

It would have been obvious for one of ordinary skill in the art at the time of the invention to combine the administration of alpha-galactosidase A protein as taught by Shiffmann and Desnick with a vector encoding alpha-galactosidase A as taught by Ziegler to a subject with a Fabry disease because either administration of alpha-galactosidase A protein or administration of a vector encoding alpha-galactosidase A can reduce globotriaosylceramide level in a subject with Fabry disease and Selden discusses that both gene therapy and enzyme replacement therapy can be used to treat Fabry disease patient and "individuals with alpha-gal A deficiencies **may also be** treated with purified alpha-gal A (i.e. enzyme replacement therapy)". Even if Selden does not specifically points out combination of gene therapy and enzyme replacement therapy for Fabry

disease, however, since either administration of alpha-galactosidase A protein or a vector encoding alpha-galactosidase A can reduce globotriaosylceramide level in a subject with Fabry disease, it would have been obvious for one of ordinary skill to combine alpha-galactosidase A protein and a vector encoding said protein so as to reach greater reduction of globotriaosylceramide level in a subject with Fabry disease. Administration of the alpha-galactosidase A protein before, after, simultaneously, or alternately with a vector encoding alpha-galactosidase A to the subject would be obvious to one of ordinary skill because determining effective schedule of administration is routine optimization of a result-effective variable and is obvious to a person of ordinary skill.

One having ordinary skill in the art at the time the invention was made would have been motivated to combine the administration of alpha-galactosidase A protein before, after, simultaneously, or alternately with a vector encoding alpha-galactosidase in order to achieve higher and greater reduction of globotriaosylceramide content in the subject with Fabry disease with reasonable expectation of success according to the teachings of Shiffmann, Desnick, Ziegler and Selden.

Applicants argue that Schiffman, Desnick, or Ziegler do not provide motivation to combine gene therapy with enzyme replacement therapy because Ziegler teaches gene therapy provides a long term therapy for treating Fabry disease, however, Desnick and Schiffmann teach that enzyme replacement therapy only provides short term results (amendment, p. 6-9). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 103(a) rejection. Selden reports that both gene therapy and enzyme replacement therapy can be used to treat Fabry disease patient and "individuals with alpha-gal A deficiencies may also be treated with purified

alpha-gal A (i.e. enzyme replacement therapy)". Even if Selden does not specifically points out combination of gene therapy and enzyme replacement therapy for Fabry disease, either administration of alpha-galactosidase A protein or a vector encoding alpha-galactosidase A can reduce globotriaosylceramide level in a subject with Fabry disease, therefore, one of ordinary skill would have been motivated to combine alpha-galactosidase A protein and a vector encoding said protein so as to reach greater reduction of globotriaosylceramide level in a subject with Fabry disease with reasonable expectation of success according to the teachings of Shiffmann, Desnick, Ziegler and Selden.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER